Form PTO-1449 (modified)	Atty. Docket No. INRP:104US	Serial No. 10/747,798
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant George H. Yoo	
(Use several sheets if necessary)	Filing Date: December 29, 2003	Group: 1633

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Class	Sub Class	Translation Yes/No

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	"Recombinant DNA Advisory Committee: Recombinant DNA and Gene Transfer," NIH Publisher, pp. 1-2, published on the www at http://www4.od.nih.gov/oba/rac/aboutrdagt.htm.
	C2	"Human genetics in the public interest," Center for Genetics and Society, Center for Genetics and Society, pp. 1-2, http://www.genetics-and-socicty.org/policies/us/agencies.html.
	C23	Clayman, "Clinical protocol for wild type p53 gene induction in premalignancies of squamous epithelium of the oral cavity via an adenoviral vector," Scientific Abstract, sponsored by Introgen, Inc., submitted January 8, 2001, place of publication NIH Recombinant DNA Advisory Committee meeting March 8, 2001, page 2.
	C24	Clayman, "Clinical protocol for wild type p53 gene induction in premalignancies of squamous epithelium of the oral cavity via an adenoviral vector," Non-Technical Abstract, sponsored by Introgen, Inc., submitted January 8, 2001, place of publication NIH Recombinant DNA Advisory Committee meeting March 8, 2001, page 3.
	C95	"Clinical protocol for wild tupe p53 gene induction in premalignancies of squamous epithelium of the oral cavity via an adenoviral vector," Investigator Gary Clayman, Sponsor Introgen Therapeutics, PowerPoint presentation, presented at NIH Recombinant DNA Advisory Committee meeting March 8, 2001.

25626549.1

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

new diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Compliance with the NIH Guidelines is ensured at the local level by Institutional Biosafety Committees (IBCs), which are registered with the Office of Biotechnology Activities. Many experiments are thus reviewed and approved by the IBCs without any input from the RAC. In addition, the RAC advises the NIH Director and his/her staff in a number of activities, including the preparation of materials required in legal actions, international coordination of biotechnology regulations, and the review of regulations proposed by other Federal agencies.

In summary, the RAC serves a critical role in the oversight of Federally funded research involving recombinant DNA. While its workload has varied over the years as the regulatory agencies have begun to review products developed for commercial purposes, the RAC continues to provide invaluable advice concerning advances in recombinant technology, new organisms under investigation, and public attitudes associated with research in molecular biology.

OBA Home | Search | Related Sites | E-mail OBA
Latest News | About RAC | NIH Guidelines | Meetings | Documents | Clinical Trials

Page Updated 03/29/00

C1

Recombinant DNA Advisory Committee

Recombinant DNA and Gene Transfer

Latest News
NIH Guidelines
Meetings and Conferences
Documents
Clinical Trials
OBA Home

The Recombinant DNA Advisory Committee (RAC) was established on October 7, 1974, in response to public concerns regarding the safety of manipulation of genetic material through the use of recombinant DNA techniques. As described in its charter, the RAC is advisory to the Director, NIH. At that time, it was thought that, "The use of this technology has various possible hazards because new types of organisms, some potentially pathogenic, can be introduced into the environment if there are no effective controls."

The RAC developed a set of Guidelines that were first published in 1976 and have been revised periodically since then. These Guidelines include a comprehensive description of facilities and practices intended to prevent unintended release or inadvertent exposure to either genetically modified organisms or recombinant DNA. Compliance with the Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA.

The RAC is a technical committee whose goal is to consider the current state of knowledge and technology regarding recombinant DNA. This includes review of human gene transfer trials, and an assessment of the ability of DNA recombinants to survive in nature and the potential for transfer of genetic material to other organisms. It also considers hypothetical hazards and methods for monitoring and minimizing risks. Approximately one-third of the 15 members do not have scientific expertise but represent public interests and attitudes. This balance is intended to provide a forum for open public debate of social and scientific issues attendant to recombinant DNA research. The RAC has been overwhelmingly successful in achieving this goal.

As described above, a major role for the RAC is to examine clinical trials that involve the transfer of recombinant DNA to humans. Currently, all human gene transfer trials in which NIH funding is involved (either directly or indirectly) are registered with the RAC. Protocols that contain unique and/or novel issues are discussed in a public forum. Factors that may contribute to public discussion of a protocol by the RAC include: (i) new vectors/new gene delivery systems, (ii)

The Food and Drug Administration (FDA) and the Recombinant DNA Advisory Committee (RAC) have jurisdiction over limited aspects of human genetic research. Adequate control over the new human genetic technologies will require new structures of regulatory authority.

The Food and Drug Administration (FDA)

The FDA claims jurisdiction over human cloning but the extent of its authority is unclear. By law the FDA must base its decisions on the safety and efficacy of a proposed product or practice and is prohibited from considering ethical or social factors.

During the 1998 Senate debate on cloning, one of the arguments for postponing legislative action was the FDA's assertion that they would use their authority to stop any attempts to create human clones.

The FDA's claim is based on the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. Under these statutes, implementing FDA regulations, clinical research on the creation of a human being using cloning technology could proceed only when an investigational new drug (IND) application was in effect. Approval of such an application would require the investigators to demonstrate that human subjects involved in such experiments would not be exposed to "unreasonable and significant risk of illness or injury." The FDA indicated in 1998 that since major safety questions associated with human cloning remained, they would not permit any such project to proceed.

The FDA does have limited jurisdiction over inheritable genetic modification, since it must approve all proposals involving human gene transfer. However, universities, clinics, and private firms are not prohibited from most types of human genetic

firms are not prohibited from most types of human genetic experimentation, including germline modification and cloning, if they use their own funds.

Back to top

Recombinant DNA Advisory Committee (RAC)

The Recombinant DNA Advisory Committee (RAC) is an advisory body appointed by the Director of the National Institutes of Health. It is charged with review of human gene transfer experiments. In the late 1980s a Human Gene Therapy Subcommittee was established specifically to explore the social and ethical implications of somatic gene transfer studies. Approval of somatic cell studies had to be obtained by both the Subcommittee as well as the parent Committee. This Subcommittee was disbanded in the early 1990s after repeated complaints by research scientists that approval from both committees was redundant. The role of the RAC has since been further weakened and is presently unclear.

Back to top

Off-Site Links

▨ Food and Drug Administration:

- Home page
  http://www.fda.gov
- Center for Biologics Evaluation and Research, "Use of Cloning Technology to Clone a Human Being"
  http://www.fda.gov/cber/genetherapy/clone.htm
- Public Health Service Act
  http://www.fda.gov/opacom/laws/phsvcact/phsvcact.htm
- Federal Food, Drug, and Cosmetic Act
  http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm

▨ Recombinant DNA Advisory Committee
http://www4.od.nih.gov/oba/rac/aboutrdagt.htm

Date modified: August 28, 2002

Scientific Abstract

Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity via an Adenoviral Vector

Principal Investigator: Gary Clayman, M.D.

A discreet group of patients with preneoplastic lesions of the oral cavity exists for which we have no meaningful treatment other than conventional surgical approaches. Unfortunately, conventional surgery does not take into account the multifocality of these processes as well as the high incidence of recurrence and 2nd primary lesions involving aerodigestive tract sites. Biochemoprevention approaches in preneoplastic lesions of the oral cavity site have demonstrated disappointing results with more than 50% of patients progressing in our prospective trial of cisretinoic acid, alpha interferon and alpha tocopherol. Biomarker studies have suggested that those patients with mutant p53 and genetic instability were at greatest risk of progression. The objective of this research is to directly modify the precancerous cell to express large quantities of an exogenously introduced, normal tumor suppressor gene product that may reverse the premalignant process by inducing apoptosis in the cancer predisposed cells, allowing for re-population with normal genotype and phenotype epithelial cells. Our goal is to determine the transduction efficiency of adenoviral mediated wild type p53 gene transfer in premalignancies of the upper aerodigestive tract and to determine the efficacy of single agent adenoviral mediated wild type 5 3 gene transfer in reversing oral premalignancies.

Patient eligibility includes males and females 18 years of age and older with clinical evidence and histologically confirmed diagnosis of mild - severe dysplasia or carcinoma in-situ of the oral cavity. Patients may have received conventional treatment for a prior head & neck malignancy, but must have a life expectancy of at least 12 months and a Zubrod performance status of <2. Female patients of childbearing potential must have a negative serum pregnancy test. Male and female patients must agree to use barrier contraception while on study, and to avoid pregnancy for 1 year after treatment. Patients must have negative serology for the Human Immunodeficiency Virus. Adequate bone marrow function (peripheral absolute granulocyte count of 2,000/mm^3 and platelet count of 100,000/mm^3), adequate liver function (bilirubin <1.5 mg/dl), and adequate renal function (creatinine 1.5 mg/dl) are required for participation. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study in keeping with the policies of the institution.

Patients will receive an Ad5 CMV p53 injection and oral rinse on day 1 followed by twice-daily oral rinses on days 2-5 in addition to lab work, research blood draws, and photo documentation for the completion of one cycle. The study cycle will be repeated on a monthly basis for a period of six months. This is a limited dose escalation study. A total of 12 patients will be entered into the phase I dose-finding trial with 33 patients anticipated to be entered into the phase II trial. Biopsies of normal and preneoplastic tissue are performed at pretreatment and two hours following the last A.M. oral rinse of the 1st and 6th cycles. Alternative biologic endpoints will also be monitored through the collection of serum and urine. Maximal transduction rate will be determined by immunohistochemistry of p53 and downstream gene products.

Non-Technical Abstract

Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity via an Adenoviral Vector

Principal Investigator: Gary Clayman, M.D.

Surgery is the only meaningful treatment currently available for persons with pre-cancerous lesions of the oral cavity. Unfortunately, conventional surgery does not necessarily prevent the condition from returning or developing into cancer. Earlier studies have suggested that patients with a mutated p53 gene are at greatest risk with up to 50% progressing to cancer despite prevention approaches. The goal of this clinical research study is to see if a normal copy of the p53 gene can be placed inside a patient's pre-cancerous cells using a virus similar to those which cause the common cold. It is hoped that this will cause the cells that may be capable of changing into cancer cells to die or return to a more "normal" state.

Patient eligibility includes males and females 18 years of age and older with a confirmed diagnosis of mild - severe dysplasia or carcinoma in-situ of the oral cavity. Patients may have received conventional treatment for a prior head & neck malignancy, but must have a life expectancy of at least 12 months and a Zubrod performance status of <2. Female patients of childbearing potential must have a negative serum pregnancy test. Male and female patients must agree to use barrier contraception while on study, and to avoid pregnancy for 1 year after treatment. Patients must test negative for the Human Immunodeficiency Virus. Adequate bone marrow function (peripheral absolute granulocyte count of 2,000/mm^3 and platelet count of 100,000/mm^3), adequate liver function (bilirubin < 1.5 mg/dl), and adequate renal function (creatinine 1.5 mg/dl) are required for participation. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study in keeping with the policies of the institution.

Twelve patients will be entered into the phase I dose-finding trial with 33 patients anticipated to be entered into the phase II trial. Patients will be asked to receive tests and biopsies before beginning treatment. Patients will receive p53 in one of three possible dosages by injection and oral rinse on day 1 followed by twice-daily oral rinses on days 2-5 in addition to lab work, research blood draws, and photo documentation for the completion of one cycle. The study cycle will be repeated on a monthly basis for a period of six months. Small tissue samples (biopsies) are taken during this time to monitor changes in the pre-cancerous cells, and to look for changes in the surrounding tissue. Urine and blood samples will also be studied in an effort to evaluate the treatment's effect.

C95

Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity via an Adenoviral Vector

Primary Investigator: Gary Clayman M.D.

Sponsor: Introgen Therapeutics, Inc.

INTROGEN

RPR/INGN 201 (Ad5CMV-*p53*)

- Adenoviral vector expressing p53
- Completely sequenced
- CGMP Manufacturing in validated clean-room facility by experienced personnel
- Final product testing in compliance with CGMP and current industry practice

INTROGEN

Previous Human Exposure to RPR/INGN 201 (Ad5CMV-*p53*)

- In use in human clinical trials since 1995
- Over 480 people exposed by various routes of administration
- Head & Neck phase III trials actively ongoing
- Phase I & II trials ongoing in additional indications
- Large safety database for this material

INTROGEN

Protocol Description

- Combination of intramucosal injection of RPR/INGN 201 (Ad5CMV-*p53*) in area of lesion followed by a series of oral swishes with same
- Patients participate in protocol for 6 months, each 1 month cycle begins with 5 days of exposure to RPR/INGN 201 (Ad5CMV-*p53*)

INTROGEN

Protocol Description: Day 1

- Lesion will be injected with RPR/INGN 201 (Ad5CMV-*p53*)
- Biopsy of lesion and contralateral region after 2 hours
- 10% acetic acid rinse for 2 minutes
- RPR/INGN 201 (Ad5CMV-*p53*) swish for 30 minutes

INTROGEN

Protocol Description: Day 2-4

- 10% acetic acid rinse
- RPR/INGN 201 (Ad5CMV-*p53*) swish and spit
- Minimum 2 hour observation
- Repeat rinse and swish/spit

INTROGEN

Protocol Description: Day 5

- 10% acetic acid rinse
- RPR/INGN 201 (Ad5CMV-*p53*) swish and spit
- Minimum 2 hour observation
- Biopsy of lesion and contralateral region
- Repeat rinse and swish/spit

INTROGEN

Special Protocol Testing Summary
Pre Treatment

- p53 genotype of microdissected lesion
- HPV of microdissected lesion
- H&E on all biopsy specimens
- TUNEL on lesion & contralateral region
- CAR on lesion & contralateral region
- p53 IHC on contralateral region only
- Antibody to serotype 5 adenovirus in serum

INTROGEN

Special Protocol Testing Summary
Post Treatment

- H&E on lesion & contralateral region
- TUNEL lesion & contralateral region
- CAR lesion & contralateral region
- p53 IHC on contralateral region

INTROGEN

RAC Reviewer Protocol Questions

- Risk to benefit ratio
- Efficacy evaluations
- Safety of acid rinse
- 30 minute duration of swish
- Consenting process

INTROGEN

Risk to benefit ratio

INTROGEN

Disease Characteristics

- Patients diagnosed with a preneoplastic lesion of the oral cavity will progress to a malignant state, most within six months.
- Surgery is frequently not effective because of diffuse, multifocal nature of these lesions.
- Patients eligible for this trial will have failed other approaches being tested.

INTROGEN

Why this study, Why this patient population

- Two Case Studies

INTROGEN

Case Study #1

- Prior history of multiple surgical procedures for removal of retromolar area lesions
- 1986 diagnosis mild dysplasia in multiple locations in oral cavity
- 1988 treatment with topical Retin A gel, discontinued because of patient discomfort

INTROGEN

Case Study #1 (continued)

- Aug 1993 carcinoma in situ, surgically removed, margins pathologically free of cancer
- Nov 1993 moderate to severe dysplasia in same area, lesion removed by laser ablation

INTROGEN

Case Study #1 (continued)

- Feb 1994 moderate dysplasia in same area
- July 1994 continued inflammation & dysplasia, Biochemoprevention therapy
- Dec 1994 continued inflammation & dysplasia

INTROGEN

Case Study #1 (continued)

- April 1996 Invasive squamous carcinoma
- May 1996 Resection of major portions of oral cavity, margins pathologically free of cancer
- May 1996 Post operative radiation therapy
- July 1996 Extensive local, facial and infratemporal fossa recurrence treated with chemotherapy and radiotherapy
- Sep 1996 Patient died of disease

INTROGEN

Case Study #2

- June 1992 Premalignant left oral lesion surgically removed, recurrence within six months
- Feb 1994 Laser ablation to remove left oral tongue premalignant lesion, recurrence within six months
- May 1996 biopsy shows mild to moderate dysplasia + hyperkeratosis of left oral tongue
- July 1996 Biochemoprevention studies initiated

INTROGEN

Case Study #2 (continued)

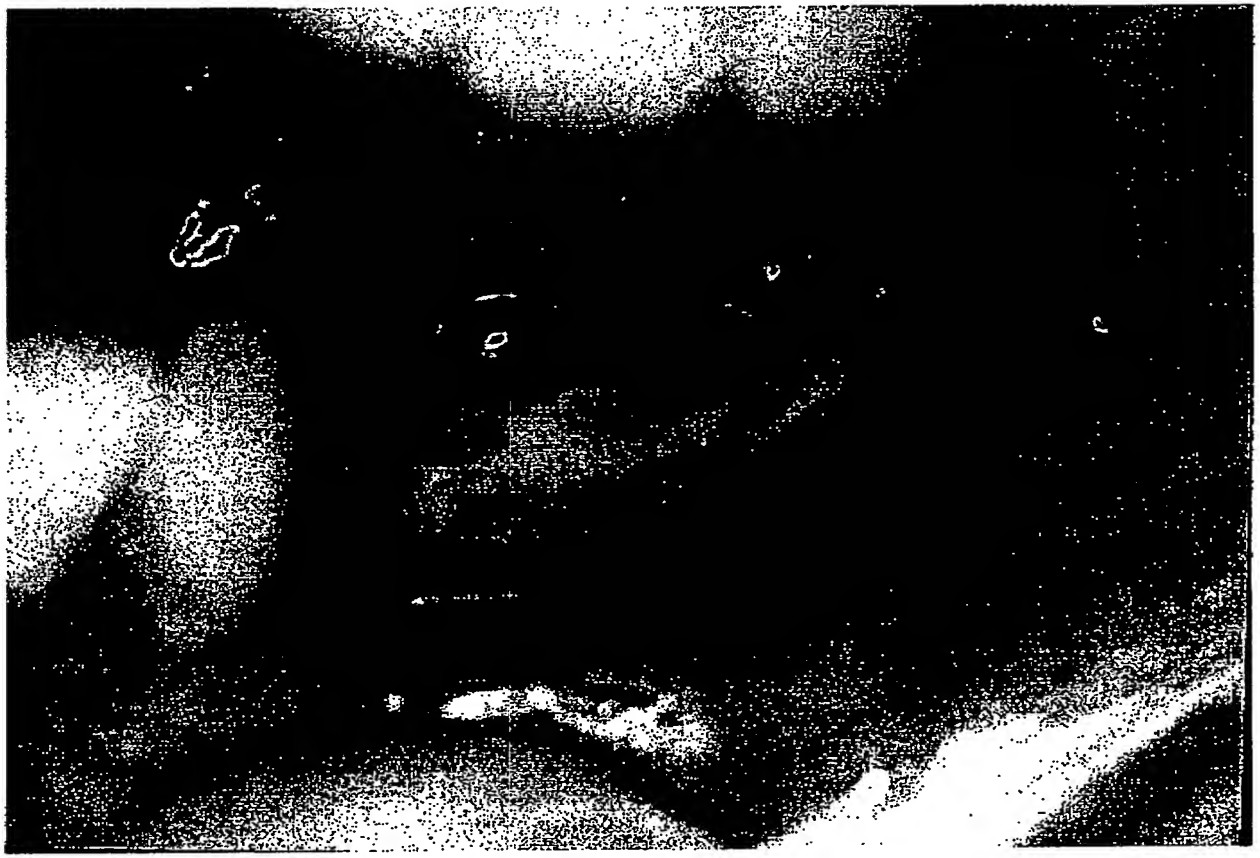
- Jan 1997 continued left oral tongue dysplasia
- Dec 1997 new lesion on right oral tongue; surgery to remove part of tongue, floor of mouth and neck. Laser ablation to clear a larger area. Margins free. Patient ineligible for biochemoprevention since he developed lesion while on that attempted prevention approach
- Feb 2001 Patient has dysplasia in two areas of oral cavity

INTROGEN

Diagnosis: Leukoplakia without dysplasia of the Oral Cavity

INTROGEN

Diagnosis: Erythroplasia with severe dysplasia of the Oral Cavity



INTROGEN

Diagnosis: Preneoplastic Lesion of the Oral Cavity

INTROGEN

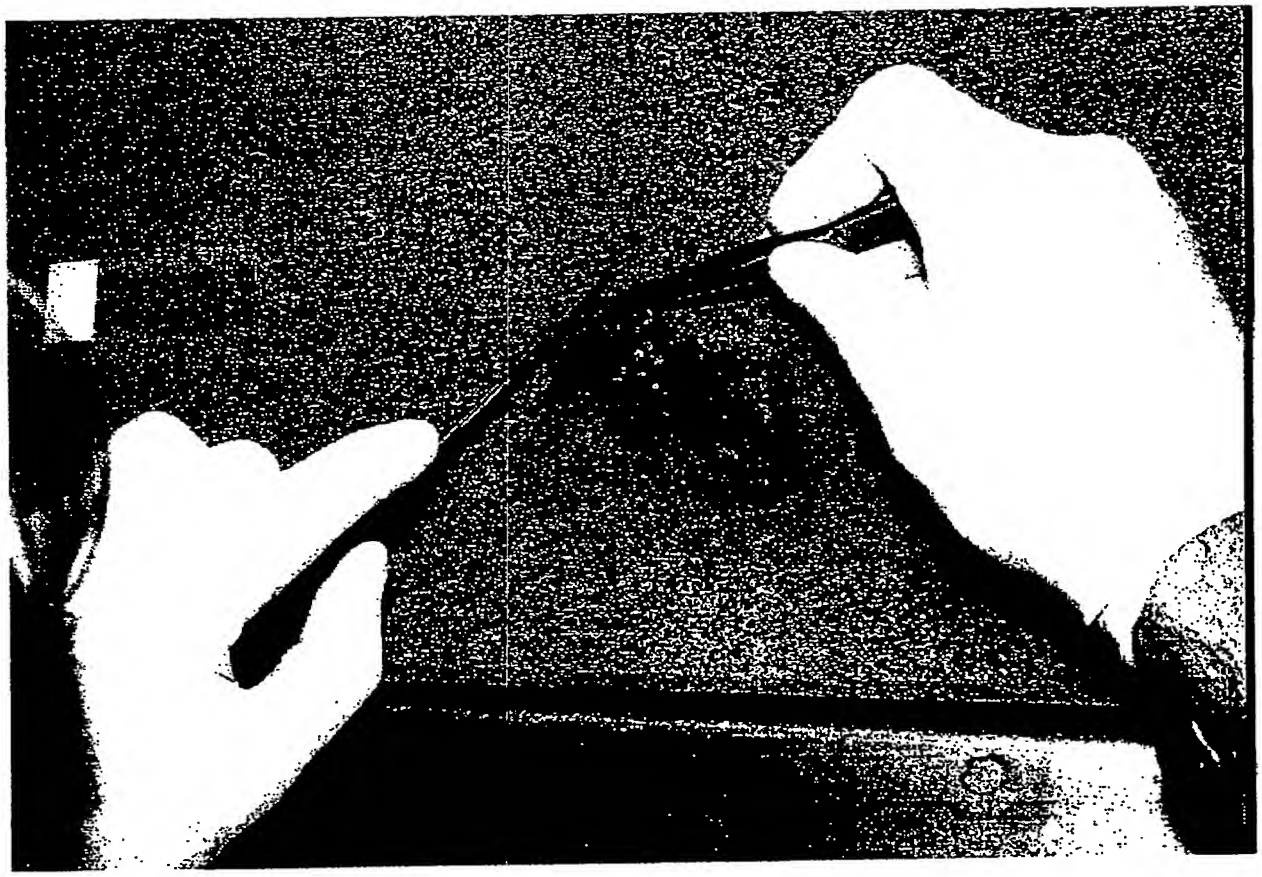
Progression to Malignant Lesion

INTROGEN

Surgical removal of carcinoma *in situ*

INTROGEN

Comprehensive pathologic analysis of premalignant lesion



INTROGEN

Extensive surgical margin required for premalignant lesion

INTROGEN

Efficacy Evaluation versus Protocol Goals for a Phase I/II Clinical Trial

- As with all Phase I/II clinical trials, the primary objective is to evaluate safety
- Any scientific information gathered is a secondary objective
- Any efficacy information that comes from a phase I/II is a secondary objective

INTROGEN

Previous Routes of Administration for RPR/INGN 201 (Ad5CMV-*p53*)

- Intratumoral in Head & Neck
- Lavage in Lung
- Intratumoral in Lung
- Intratumoral in prostate, ovary, breast, bladder
- IV

INTROGEN

Safety of Acid Rinse

- 10% acetic acid approximately the strength of household vinegar (6%)

INTROGEN

pH Comparison

Item	FDA or USP acceptable pH range	Example of tested pH
10% acetic acid	N/A	2.2
Coca Cola	N/A	2.3
Sauerkraut	3.4-3.6	3.3
Grapefruit juice	3.0-3.3	3.5

INTROGEN

Questions on
30 minute duration of swish

- Route of administration
- Safety for other tissues
- Potential for aspiration

INTROGEN

30 minute duration of swish

- Common route of administration
- Used for Tingel, approved flouride compound
- Not uncomfortable for patients
- Will be performed under clinical observation

INTROGEN

Previous Routes of Administration to Head & Neck

- Intratumoral and intramucosal injections in multiple head and neck sites
- Intraoperative injection and lavage into surgical beds
- Intraoperative injection into mucosal margins following cancer removal

INTROGEN

Previous of Administration to Lung

- Bronchoalveolar lavage in Lung
- Intratumoral in Lung

INTROGEN

Additional Previous Routes of Administration

- Intraprostatic injection
- Intervesicle in bladder
- Intravenous
- Intraperitoneal in ovary
- Intratumoral in breast

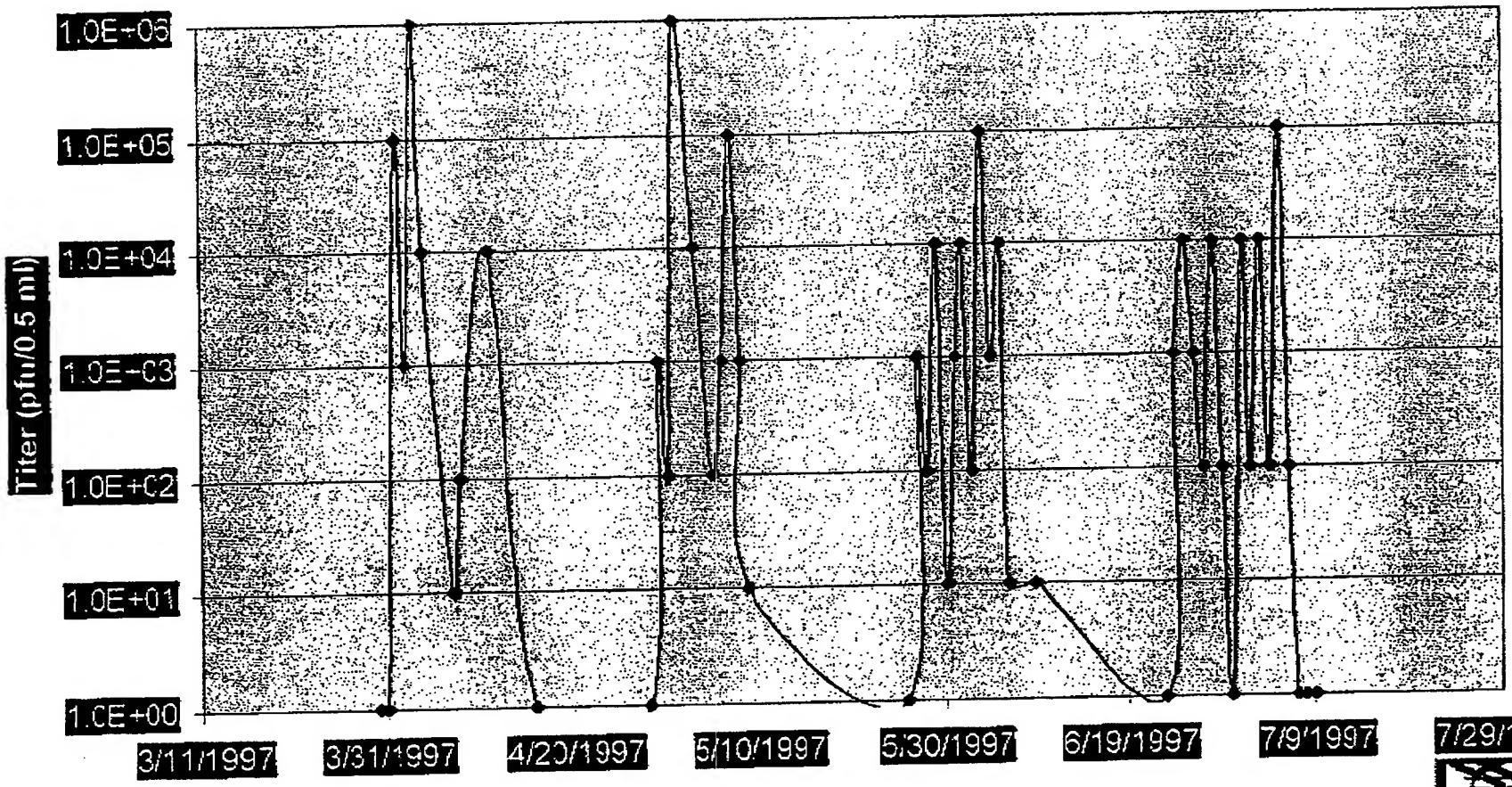
INTROGEN

RPR/INGN 201 (Ad5CMV-*p53*): Safe for normal tissue?

- Not toxic to non-malignant structures
- Post-surgical injection into healthy surgical beds of the Head and Neck and oral cavity
- Intraprostatic injection exposed normal prostate tissue
- Lavage of cerebral cortex exposed normal brain tissue
- All routes tested thus far are well tolerated

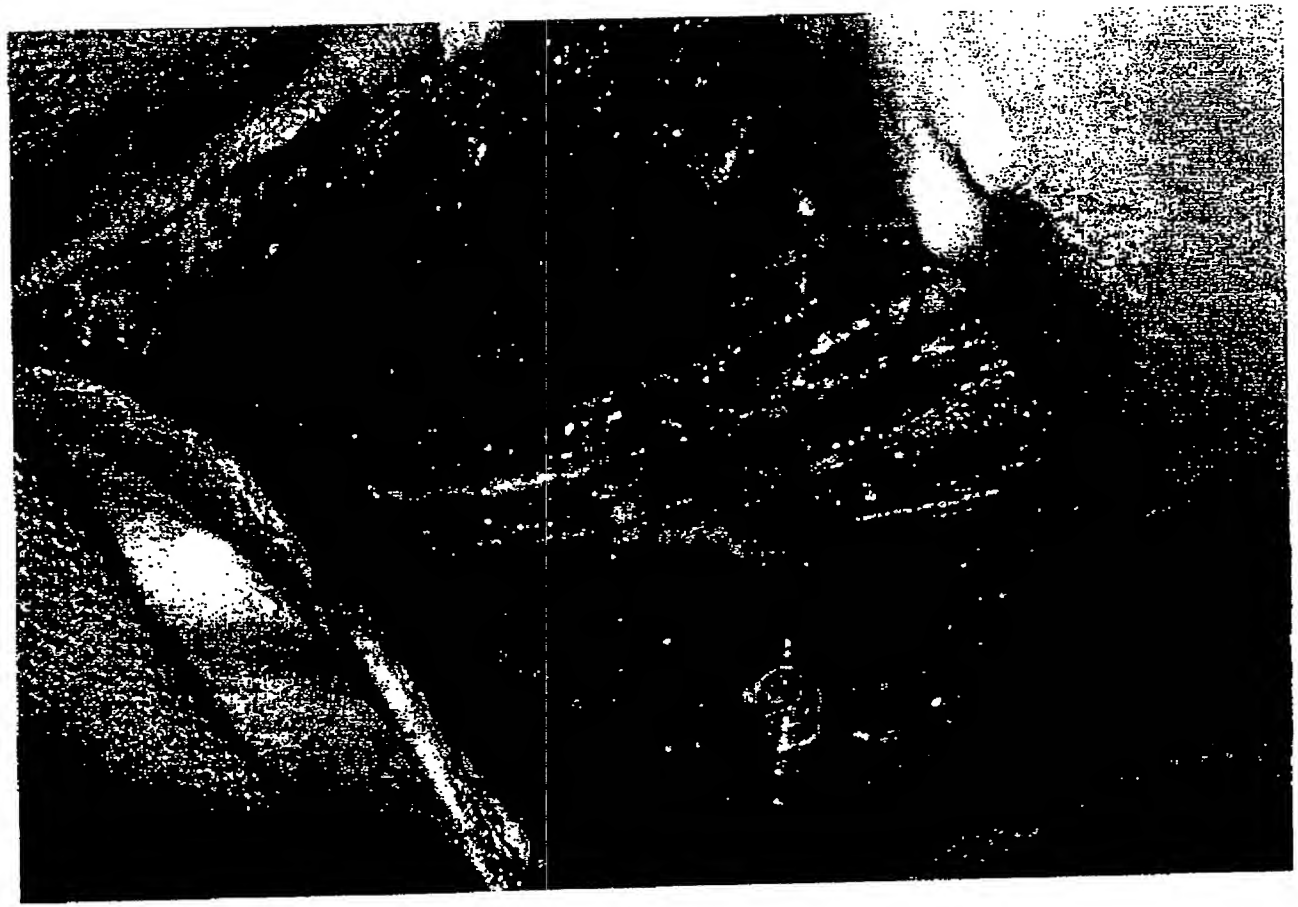
INTROGEN

RPR/INGN 201 in Upper Aerodigestive Tract Secretions Following Intratumoral Administration



INTROGEN

Post surgical injection into healthy surgical bed



INTROGEN

Informed Consent

- Viewed by investigator and sponsor of this trial as a process beyond obtaining appropriate signature
- Witness required by IRB to observe the informed consent process
- Important gene transfer considerations included

INTROGEN